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EXCEPTIONAL CASE

A patient with chronic kidney disease, primary biliary cirrhosis and metabolic acidosis

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ABSTRACT

Autoimmune disorders such as rheumatoid arthritis or Sjögren's syndrome can be associated with impaired renal acid excretion. Only few cases of patients with primary biliary cirrhosis (PBC) and distal renal tubular acidosis (dRTA) have been described. Here, we present the case of a 60-year-old woman with PBC and dRTA. Her kidney biopsy showed an absence of markers of acid-secretory Type A intercalated cells (A-ICs) and expression of aquaporin-2, a marker of principal cells, in all cells lining the collecting duct. Moreover, the serum of the patient contained antibodies directed against a subset of cells of the collecting duct. Thus, PBC-related autoantibodies may target acid-secretory A-ICs and thereby impair urinary acidification.

Keywords: acidosis, autoantibodies, dRTA, intercalated cells, primary biliary cirrhosis

INTRODUCTION

Renal tubular acidosis (RTA) is caused by impaired ability of the kidney either to regenerate bicarbonate from ammoniogenesis or to excrete acids and increase urinary acidification. The latter function can be disturbed in syndromes of distal renal tubular acidosis (dRTA). Type I RTA or dRTA can be caused by inherited mutations in genes encoding the anion exchanger 1 (AE1) anion exchanger (SLC4A1), the $\alpha 4$ and B1 H^+ -ATPase subunits (ATP6V0a4 and ATP6V1B1) or the forkhead transcription factor (Figure 1) [1–2]. Acquired forms of dRTA can be due to various drugs or are often observed as part of the various autoimmune disorders including Sjögren's syndrome, rheumatoid arthritis and possibly also primary biliary cirrhosis (PBC). In biopsies of

some of these patients, the absence of H^+ -ATPase staining in the collecting duct was reported [3–7].

Here, we report the case of a 60-year-old female patient with PBC and dRTA and the absence of markers of intercalated cells in her kidney biopsy. To our knowledge, this is the first case of PBC with dRTA and with a detailed analysis of the kidney biopsy.

CLINICAL CASE

A 60-year-old woman was admitted because of progressive chronic kidney disease. On admission, she had a creatinine of $171 \mu\text{mol/L}$ [estimated glomerular filtration rate of 28 mL/min/

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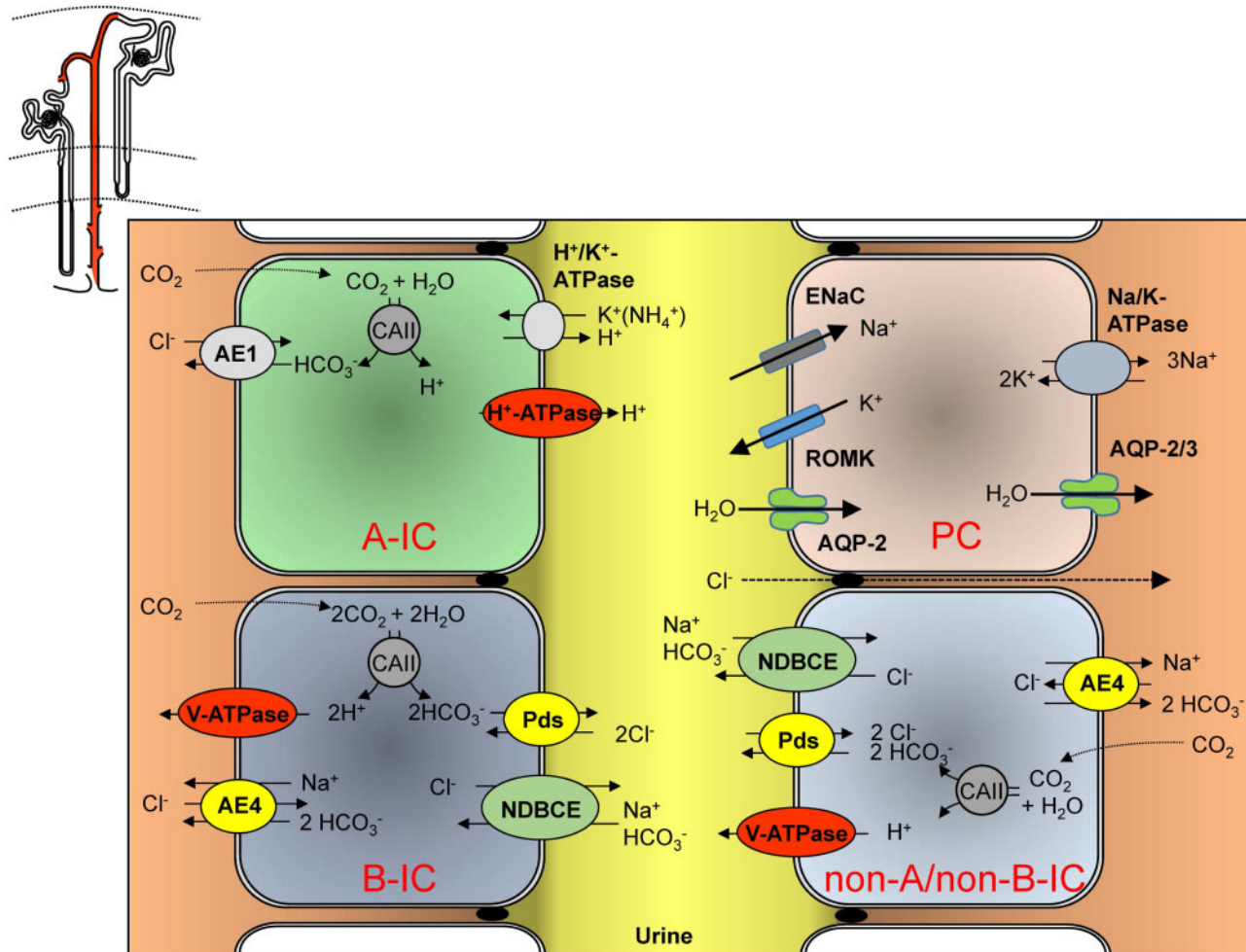


FIGURE 1: Scheme depicting the different types of cells in the collecting duct and their specific markers. PCs express the AQP2 water channel together with the ENaC Na^+ - and ROMK (Renal Outer Medullary K^+ -channel) K^+ -channel. Acid-secreting A-ICs express the basolateral AE1 and luminal H^+ -ATPases containing the B1 and a4 subunits. Bicarbonate-secreting Type B and non-A/non-B intercalated cells (B-IC and non-A/non-B-IC) express pendrin (Pds) and the Na^+ -dependent bicarbonate-chloride exchanger (NDBCE), and either basolateral (B-IC) or luminal (non-A/non-B-IC) H^+ -ATPases also containing B1 and a4 subunits. All types of ICs express CAII.

1.73 m^2 (CKD-EPI)] and microalbuminuria. The urine dipstick was positive for leucocytes but not for erythrocytes. Her urinary sediment was normal, as was her physical examination. There were no signs of a systemic disease and no oedema.

Her past medical history was unremarkable apart from hypertension, for which she was taking amlodipine, and PBC. The latter was treated with ursodeoxycholic acid and enterically coated with budesonide. She tested negative for antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, rheumatoid factor and antibodies against SS-A and SS-B. IgM antibodies were slightly elevated (5.72 g/L, normal range: 0.4–2.4 g/L), anti-mitochondrial antibody (AMA) titres were >2560 (normal <80).

A renal biopsy showed active tubulointerstitial nephritis and signs of hypertensive renal disease (Figure 2).

Blood gas analysis was performed. Her pH was 7.23 with bicarbonate of 11.1 mmol/L and a pCO_2 of 27.5 mmHg. Her anion gap was normal with a value of 11.9 mmol/L (Na^+ 140 mmol/L, K^+ 3.3 mmol/L, Cl^- 117 mmol/L). Taken together, these data indicate a normal anion gap metabolic acidosis and hypokalaemia.

Her urinary pH was 7.0, urinary-specific gravity was 1.005 g/mL and the urinary anion gap (UAG) was positive ($\text{UAG} = \text{U}_{\text{Na}} + \text{U}_{\text{K}} - \text{U}_{\text{Cl}} = 55 \text{ mmol/L} + 18.5 \text{ mmol/L} - 41 \text{ mmol/L} = 32.5 \text{ mmol/L}$).

We concluded that our patient had dRTA. The patient did not have diarrhoea, and there was no evidence for the use of laxatives.

The association of PBC and RTA has been described before [8–14] and one study [15] also speculated about the pathophysiology of the RTA.

Kidney biopsy sections were stained with antibodies against the AE1 [16], in kidney specifically expressed in acid-secreting type A intercalated cells (A-ICs) (Figures 1 and 2) (for methods see Supplementary information). It is also expressed in red blood cells. Sections were co-stained with antibodies against the B1 H^+ -ATPase subunit [17] (also highly enriched in A-ICs) and against the AQP2 water channel expressed in neighbouring principal cells (PCs) (Figures 1 and 2). While strong staining for AE1 and the B1 H^+ -ATPase subunit was found in cells of the collecting duct system in biopsies from healthy control kidneys ($n=4$ independent kidneys), no staining was detectable in the patients biopsy. Of note, AE1 still stained red blood cells present in the biopsy (Figure 3A and B). In another set of biopsies stained for the a4 H^+ -ATPase subunit [18], enriched in all subtypes of ICs, and for the AQP2 water channel, no staining for a4 in cells of the collecting duct system was detectable, whereas all cells were positive for AQP2 (Figure 3C and D).

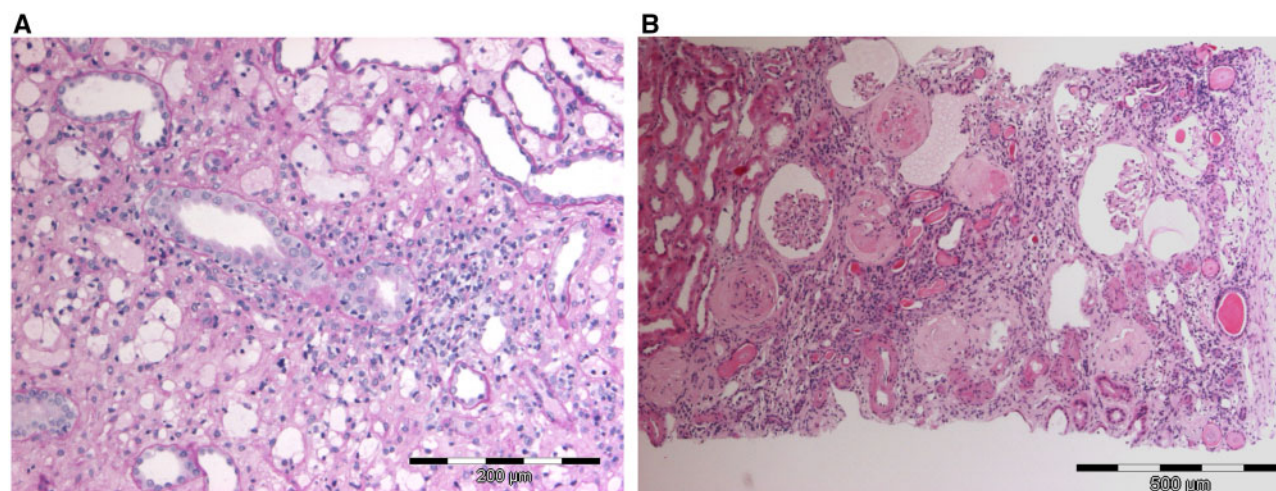


FIGURE 2: (A) H&E- and (B) PAS-stained kidney biopsy from patient showing obliterated glomeruli, inflammatory infiltrates, intratubular hyaline cylinders, tubular atrophy and dilatations and interstitial oedema consistent with active tubulointerstitial nephritis.

In the last set of experiments, kidney sections from healthy donors were incubated with either serum from the patient (1:200) or with sera obtained from healthy controls ($n = 4$). Subsequent addition of anti-human IgG fluorescent labelled antibodies allowed to detect IgG antibodies. In the kidney sections incubated with control sera, no IgG-related staining could be detected, whereas the patient's serum produced a distinct labelling of the apical pole of a subset of cells in the collecting duct. Some of these cells were also positive for AQP2 or AE1, suggesting the presence of autoantibodies against principal and A-ICs in the patients serum (Figure 3E and F).

DISCUSSION

dRTA can be caused by various autoimmune disorders. While the relative high incidence of dRTA in patients with Sjögren's syndrome or rheumatoid arthritis has been well documented, far fewer reports are available about the occurrence of dRTA in patients with PBC [8, 10, 11]. The incidence of dRTA in patients with renal involvement in Sjögren's syndrome has been estimated to be up to 30% [6, 19], whereas the incidence of dRTA in syndromes of PBC is not very well studied. One study including 18 patients with PBC found dRTA in six patients (33%) [11].

Our patient showed the typical clinical symptoms of dRTA, the combination of normal anion gap hyperchloraemic metabolic acidosis and hypokalaemia with an inappropriately alkaline urine pH. Moreover, she presented with a positive UAG, suggesting impaired renal excretion of ammonium.

Her kidney biopsy showed signs of active tubulointerstitial nephritis. However, dRTA is not a typical feature of tubulointerstitial nephritis and therefore we further analysed the biopsy of the patient for alterations in the expression of markers of acid-secretory ICs. Immunohistochemical analysis revealed the complete absence of three different markers of A-ICs, the AE1 anion exchanger and the B1 and a4 H^+ -ATPase subunits that are enriched in these cells [1]. Moreover, all cells lining the connecting tubule and collecting ducts in the patient's biopsy stained for the AQP2 water channel, a marker of PCs. These findings suggest the loss of differentiated ICs from the kidney of this patient and explain the severity of acidosis.

Absence of H^+ -ATPase staining or even the complete loss of markers of ICs has been described in few cases of patients with Sjögren's syndrome and dRTA [7, 20, 21] or in a patient with autoimmune gastritis and hypothyroidism [4]. In a small series of

13 patients with tubulointerstitial nephritis specifically selected for the presence of a high number of IgM-positive plasma cells in their kidney biopsies, all patients were reported to suffer from dRTA. However, also 92% of patients had signs of renal Fanconi syndrome and four patients were found to have also Sjögren's syndrome [22]. Notably, in the biopsies of all patients, a reduced number of AE1 and E1 H^+ -ATPase subunit-positive cells were observed. Also, AMA titres were elevated.

Autoantibodies directed against ICs have been identified in few patients; however, the exact target of these autoantibodies has remained mostly elusive. In some patients with Sjögren's syndrome, the presence of autoantibodies against carbonic anhydrase II (CAII) has been reported [23, 24]. In patients with tubulointerstitial nephritis and a high number of IgM-positive plasma cells, a role of IgM and anti-mitochondrial antibodies has been discussed, but no causative role and no targets are proven yet. Our patient had elevated levels of IgM and increased titres for anti-mitochondrial antibodies.

We also detected autoantibodies in the serum of our patient, which appear to be directed against a subset of cells in the collecting duct. Cells positive for AQP2 but also cells that stained for AE1 were stained by autoantibodies, mostly at the apical pole. This pattern is not consistent with the expression of CAII, which is localized to the cytosol of all ICs but absent from PCs. It is also not consistent with the pattern of H^+ -ATPase expression in these cells or with mitochondrial targets, suggesting that other, as yet unknown proteins may be targeted by these autoantibodies.

In summary, PBC can be associated with dRTA and may be considered as a complication in managing PBC patients. dRTA is likely caused by the absence of A-ICs in the kidney. Autoantibodies were detected, but whether these autoantibodies are the cause or consequence of dRTA and tubulointerstitial nephritis is unclear.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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The biopsy was performed with informed consent under the institutional ethics protocol and the analysis of the kidney biopsies for research purposes was done with informed consent from the patient. Control kidney biopsies from normal

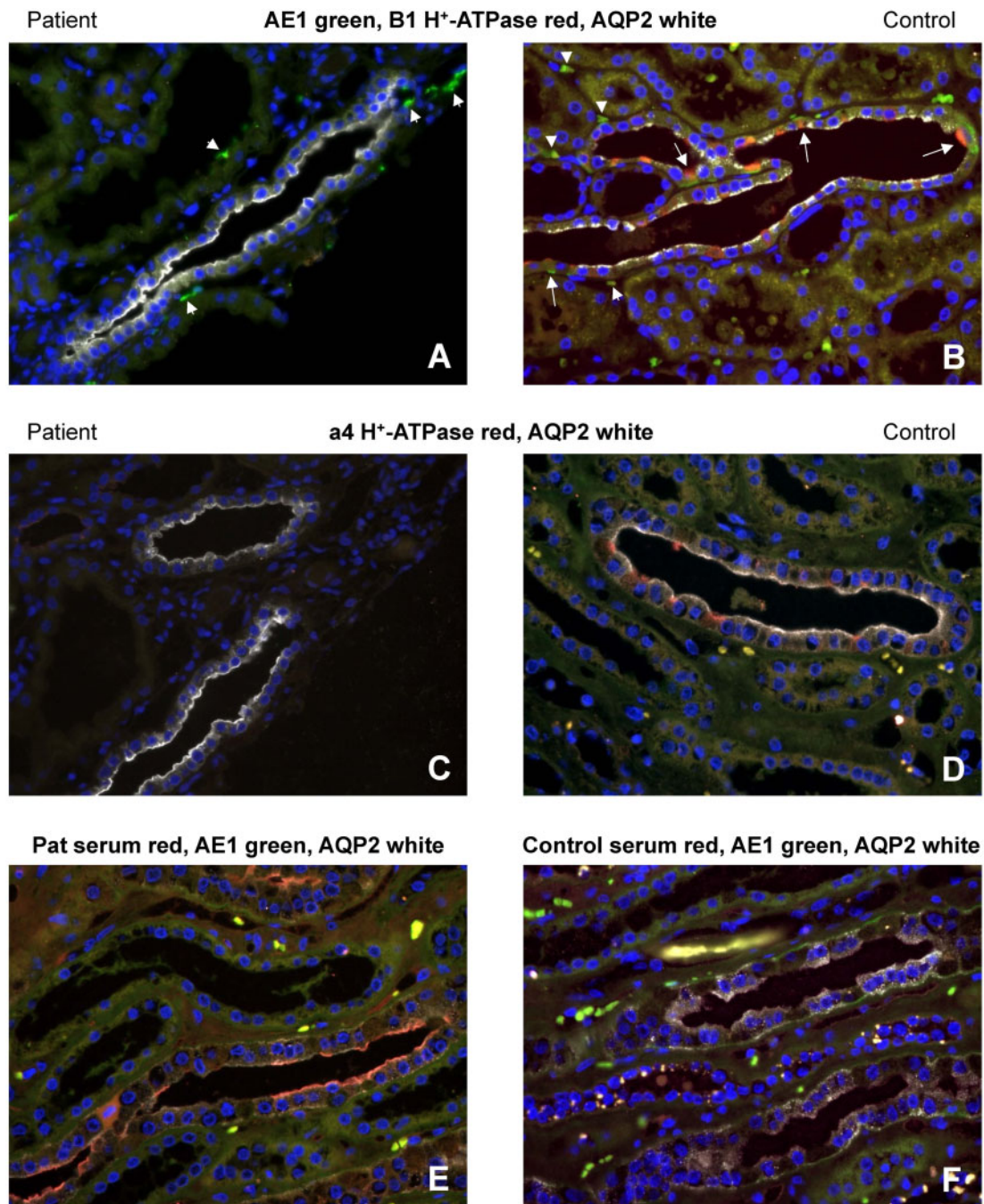


FIGURE 3: (A and B) Kidney biopsies from the patient and four independent controls were stained with antibodies against the AE1 anion exchanger (green), the B1 H⁺-ATPase subunit (red) and the AQP2 water channel (white); nuclei were stained in blue with DAPI. Arrows indicate acid-secretory ICs in control biopsy; arrow heads show red blood cells expressing AE1. (C and D) The same biopsies were also stained against the a4 H⁺-ATPase subunit (red) and AQP2 (white). (E and F) Control biopsies were incubated with the patient's serum or sera from four independent controls and human IgG detected with anti-IgG antibodies (red). Sections were counterstained with antibodies against AE1 (green), AQP2 (white) and DAPI (blue). Original magnification for all pictures $\times 400$.

kidneys were obtained from the Department of Pathology, University of Zurich, Switzerland, and used under the ethics protocol approved by the Ethics committee of the Kanton of Zurich, permission number KEK-Zh-Nr. 2012-0312.

CONFLICT OF INTEREST STATEMENT

None declared.

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